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Targeting HER2 in Biliary Tract Carcinomas: Challenges and Opportunities

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Biliary tract carcinomas (BTCs) constitute a clinically and genetically heterogeneous group of malignancies arising from the biliary epithelium. The four established clinicopathological subtypes of BTCs (intrahepatic cholangiocarcinoma, ICC; perihilar cholangiocarcinoma, PCC; distal extrahepatic cholangiocarcinoma, ECC; gallbladder cancer, GBC) show partially overlapping genomic profiles, yet the prevalence of the various molecular subgroups vary significantly between these groups (Fig. 1). ICCs show the highest abundance of targetable genomic alterations, while ECCs, PCCs and GBCs are characterized by a high prevalence of currently undruggable alterations including activating mutations in *KRAS*.

Personalized treatment for the distinct molecular subgroups of BTC is rapidly emerging, gradually shifting the treatment landscape for this difficult-to-treat tumor entity. In 2020, the FDA granted approval for pemigatinib, a selective FGFR 1–3 inhibitor, for pre-treated unresectable cholangiocarcinoma harboring genomic rearrangements of *FGFR2,* based on data from the phase II FIGHT-202 trial [1]. Both pemigatinib and infigratinib, another selective FGFR 1–3 inhibitor, are currently being evaluated against chemotherapy for 1st line treatment in phase III trials (NCT03656536, NCT03773302) [2]. FGFR2 blockade in FGFR2-altered BTCs is consistently associated with high response rates, making this approach also highly feasible for molecular conversion treatment in the curative-intent setting [3]. The second subgroup of BTCs with a clinically already advanced targeting strategy is those harboring *IDH1* hotspot mutations. For this subgroup, the phase III ClarIDHy trial showed improved progression-free survival (PFS), however not overall survival (OS), for treatment with IDH1 inhibitor ivosidenib over placebo [4]. Consequently, ivosidenib is undergoing FDA priority review in this indication. Beyond *FGFR2* and *IDH1* alterations, precision treatment for several other smaller molecular subgroups of BTC is gaining increased attention. Less common molecular subgroups include BTCs with high microsatellite instability (MSI-H) [5] and BTCs harboring oncogenic mutations with in the BRAF serine/threonine kinase [6] as well as tumors harboring mutations or amplifications of the *HER2/neu* oncoprotein.

The article by Jacobi et al. [7] within this issue reports focuses on the latter subgroup. The authors report the prevalence of *HER2/neu* genomic alterations in a large real-life cohort of BTCs and illustrate therapeutic targeting of HER2/neu in BTC by reporting 3 example cases. The HER2/neu oncoprotein is among the best established oncogenic drivers and therapeutic targets in precision oncology. Also for BTCs, HER2/neu is an attractive molecular target, particularly since – in contrast to *FGFR2* and *IDH1* alterations – HER2/neu activating mutations or copy number alterations also relatively frequently occur in PCC, ECC and GBC. In this respect, results reported by Jacobi et al. are in agreement with previously reported findings [8–10].

Despite the abundance of HER2/neu alterations and the available of a rapidly growing range of potent and selective drugs targeting HER2/neu, only limited data are available from prospective trials investigating therapeutic targeting of HER2/neu in BTCs. In the NCT02091141 ("My Pathway") phase 2 prospective study, 11 patients with BTCs harboring Her2 overexpression or amplification [8], or activating mutation [3], received a combination treatment with trastuzumab and pertuzumab. Four

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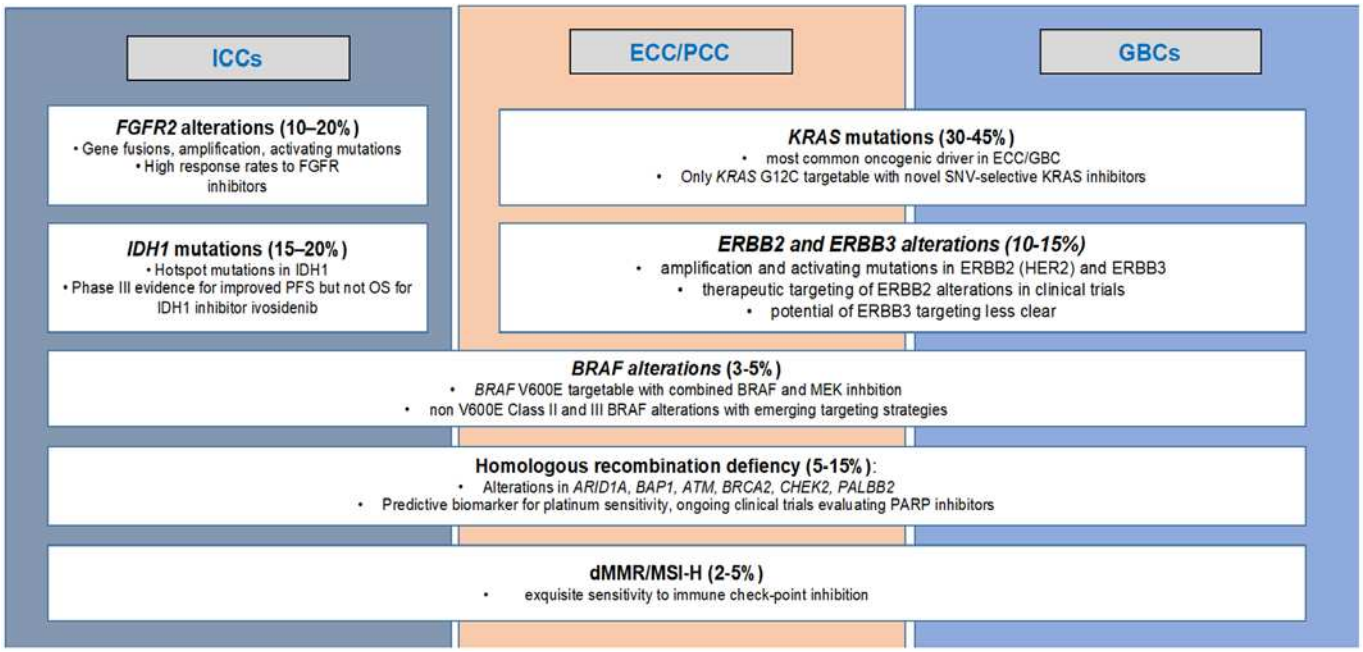

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Fig. 1. Targetable genomic alterations in distinct anatomical subtypes of biliary tract carcinoma (BTC). ICC, intrahepatic cholangiocarcinoma; PCC, perihilar cholangiocarcinoma; ECC, distal extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; dMMR/MSI-H, mismatch repair-deficient/microsatellite instability-high; HRD, homologous recombination deficiency; SNV, single nucleotide variant (modified from Akhoundova, Hussung and Fritsch, healthbook TIMES Onco Hema 2020;(5):52–59).

of these patients showed a partial response and further 3 patients stable disease for more than 4 months [11]. Further retrospective studies and case reports reported on small number of patients treated with heterogeneous combinations of Her2 antibodies +/– chemotherapy [12]. Less encouraging prospective treatment data are available for tyrosine kinase inhibitor lapatinib, evaluated in two phase 2 studies, showing lack of activity in molecular unselected patients' population [13, 14]. Two of the patients reported by Jacobi et al. [7] received oral HER2 inhibitor neratinib within a non-specified clinical trial. The phase 2 SUMMIT basket trial treated patients with BTCs harboring activating mutations in HER2/neu with neratinib, observing an objective response rate of 2/19 and disease control rate of 6/19 patients, respectively. Median PFS in this cohort was reported to be 1.8 months [15]. Trials testing newer HER2-targeting agents in BTC are ongoing including antibody-drug conjugate trastuzumab deruxtecan [16], a compound with very encouraging response rates in HER2-positive breast [17], gastric [18] and colorectal cancers [19].

While targeting HER2/neu in BTCs shows considerable promise, there are also significant limitations and unmet challenges to overcome. Thus, it remains unclear how to best distinguish in a given case between a HER2/neu oncogenic driver alterations and mere passenger events. Deciphering the role of HER2/neu in an individual tumor requires both detailed information on the alteration identified and the genetic context it occurs in. For instance, while HER2/neu amplifications in a *KRAS* wild type background are well-established targets for precision treatment, validated across several entities and with proven therapeutic potential, the oncogenic impact of activating *HER2*/neu mutations are much less clear. Similarly, the best way of targeting HER2/neu activating mutations in a given entity remains to be established [20]. From Jacobi et al. [7], we neither learn about the co-alterations found in BTCs with identified HER2/neu alterations nor essential details about HER2/neu copy numbers or HER2/neu mutation variant allele frequencies. Both critical parameters also are not routinely reported by Foundation One CDx, which in the context of HER2/neu-directed precision treatment, is a major limitation of the test.

In summary, prospective precision oncology trials establishing the best possible targeting strategies for the distinct type of HER2/neu alterations found in BTC are urgently required in order to exploit the full potential of HER2/neu targeting in BTCs. In the meantime, detailed reporting of real-world data can help to better establish a precision oncology workflow for HER2/neu testing and targeting in BTC. From a clinician's perspective, many questions remain including timing and modality of testing (tissue vs. liquid biopsy, which test?) as well as correct interpretation of results in the genomic context of a given tumor and the individual patient's clinical situation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

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